variable, minimal luminal diameter at the actual, let's say, proximal anastomosis site might be a useful observation, whether it is a primary endpoint or not.

DR. EDMUNDS: One more would be symptoms from the region at risk.

DR. WHITE: That is absolutely true, except we heard today that many of these vein grafts fail without symptoms or even very good objective measurements. So, that is the problem.

DR. EDMUNDS: That can't be the only criteria.

DR. TRACY: Dr. Zuckerman?

DR. ZUCKERMAN: The points that Dr. Krucoff made about use of MLD instead of the dichotomous endpoint of greater or less than 50 percent are very interesting, and also Dr. Bridges' point about looking at the distribution of intimal hyperplasia, etc. because potentially those endpoints can decrease your sample size, but the challenge that we have right now, until we learn more about what that means, is to choose a patency endpoint that is clinically relevant and that is why we, at the FDA, like Dr. White's idea of the 50 percent benchmark right now. But, Dr. White, can

you explain that the actual determination of that 50 percent benchmark is very dependent with vein graft disease on how you measure it, and do you have any qualifying factors here?

DR. WHITE: Yes, I would like to be the core lab!

[Laughter]

Bram is referring to the problem of what is the reference object and what is the reference segment from which you take the 50 percent diameter in a vein graft. There are obviously differences in the proximal and distal diameter of that graft and that would have to be codified. I think you would maybe even have to divide the graft into thirds, as we used to talk about, proximal, mid-body and distal regions of the graft, and we could codify the nearest normal segment of that graft to be the 50 percent measurement. The problem with that is the ostium and then you would have to take the nearest distal segment, which is obviously a different standard.

DR. EDMUNDS: Why do you seek a single outcome? My car fails in lots of ways--flat tire, motor stops, clutch falls off, all kinds of ways. So, if this proximal anastomosis blows off the

aorta, that is a failure as far as I am concerned.

DR. ZUCKERMAN: Right. If I were to summarize your comments before, I think we agree that all the endpoints that you noted must be measured and observed on the case report forms. One could generalize them into acute procedure success composite variable and chronic success composite variable measured perhaps at six months, and the six-month variable would include that measurement of greater than 50 percent patency plus perhaps B or C, but I think the 50 percent patency that Dr. White is referring to is a very important part of that chronic composite endpoint due to its clinical implications. It is where he would reintervene if it was greater than that, which is what we are interested in.

DR. BRIDGES: The other reason for the 50 percent is that the Fitz-Gibbon criteria are based on 50 percent and there is a large literature so to compare the data to that, obviously that would be a useful endpoint and several recent studies have used that classification system. So, clearly, it would be important to have that particular cut-off point.

DR. KRUCOFF: The only pitfall I would be

wary of then is if a 45 percent stenosis at 6 months is a harbinger of a 95 percent stenosis at 18 months, the dichotomous approach, if your angiographic endpoint is too early, might create a pitfall. I would just be thoughtful about combining the timing of your angiogram--if a primary endpoint is dichotomous at a clinical level, to make that the timing of your angiogram is sufficiently latent in natural history that it is appropriate.

DR. ZUCKERMAN: Again, Dr. Krucoff, you have given an analogy of the stent trials and you mentioned first in man. Does part and parcel of this need to be to show chronic stability in a smaller subset between one and two years, which was the first in man stent analogy? Another technique that we used in the stent trials is to ask for an IVIS subset study in order to show actual healing at the site of implantation. Would you like to comment?

DR. KRUCOFF: I think that is a little tougher only because now you are really instrumenting this. I think there has already been expression of concern about how far you are going to go with invasive procedures. I think it is

pretty compelling in this arena. You are going to have to go at least to an angiogram. That is my personal opinion.

I feel a little differently when it gets to full anticoagulation in order to put an interventional catheter, you know, a guide wire through the vessel and bring a device down where you are not actually planning therapeutic for the vessel. It is possible that at a later time you might eventuate a specific question to ask, Bram, but I would be concerned about over-instrumentation.

DR. HIRSHFELD: To follow-up on what Mitch just said, the more I listen to this the more I am concerned about the challenge of recruiting subjects to participate in this trial. I am not backing away from the importance of doing the trial, but I think the challenge to the sponsors and to the investigators will be to recruit a patient who is going to receive two saphenous vein grafts, and tell the patient that one of those two grafts will be treated with this new device and, as a reward for participating in this study, they get to have a cath at six months. So, it may be that there will be relatively limited incentive in the

part of patients to actually sign up for this, and it might be a real challenge to recruit for this. I think we have to weigh that consideration in addition to everything else.

DR. AZIZ: We could ask the professor from Germany, he could probably give us some insight as to how difficult it was to recruit patients. Could you give us some insight on that?

PROF. KLIMA: Could you just repeat the question for me?

DR. AZIZ: You know, there has been some concern raised that if we stay with the strict criteria and the patients need to have an angiogram that they may not want to come into the study. Did you have difficulty in recruiting patients into the trial?

PROF. KLIMA: Not at all. I think you have to real give the patient the information that you are using a new system, and even though all these devices had a CE certificate in Europe which, you know, is some kind of approval from the European governments, you have to make the point clear that this is that we do not know how it will react within the next six months, twelve months, or whatever. So, we talk to the patients before we do

the surgery and I would say that 99 percent of the patients agreed to be a part of the study.

DR. AZIZ: Also, were they sort of favorably disposed to the angiogram?

PROF. KLIMA: Well, I think that really depends on your study coordinator. I would say more than 80 percent would say yes, they will come back for an angiogram.

DR. TRACY: I think we have a lot of history of having protocols where we have had to ask patients to come back and do procedures that clinically otherwise wouldn't have been indicated. Either you can do it with a good coordinator or you can't. If you can't, then you are not going to have the patients enrolled in the study. I don't think that that is our concern here. I mean, we are trying to decide what the best design is.

DR. AZIZ: I think that question has been raised a number of times as to whether if you told a patient they are going to have an angiogram at six months how easy to would be to recruit the patients.

DR. TRACY: Well, if you can't, you can't.

DR. WHITE: I think that is a cultural issue. Having practiced in a European country, I

can tell you that the American population reacts differently than they do in Scotland and I am sure that the German population, in their relationships to their physicians, is distinct from the relationship that we have in the United States and I don't know that that translates very well.

DR. BRIDGES: I have one quick question on the study design by the professor from Hanover. Given that you hand-sewed half of the anastomoses and you used the anastomotic device for the other half, and your patients were all done on bypass I believe.

PROF. KLIMA: Yes.

DR. BRIDGES: How did you decide which graft to do first? Did you use side-biting clamp for your proximal anastomosis for the hand-sewn and then remove it and then do the Symmetry device, or did you use the Symmetry device in the presence of a cross-clam? I just wanted to know if at some point you could provide those details because those would be important details in terms of figuring out--if the committee decided to follow that sort of study design, those would be important details.

PROF. KLIMA: Yes, we did both proximal anastomosis first under the side-clamping condition

because there are several techniques out there which allow you to make a proximal anastomosis without side clamping. However, this is pretty difficult because you would have another device which you need to make a proximal anastomosis. So, we just side-clamped, made the proximal anastomosis first and then, as a consequence, we did the distal anastomosis depending on the target artery which was selected for the Symmetry device or the hand-sewn anastomosis.

DR. BRIDGES: You applied the Symmetry device with a side-biting clamp in place?

PROF. KLIMA: Yes, we did.

DR. BRIDGES: Which is a little bit different than the typical application in beating heart surgery.

PROF. KLIMA: Yes, that is correct but you can use the system also in an arrested heart situation where you make your cross-clamp, for example, and still have the opportunity to make a shot with this device. The side-clamp technique allows you to have a pretty similar situation at least for your first shot when you are doing the Symmetry anastomosis because the aorta is still filled with blood so you are able to bring the

system in, in a very similar way as you would do without side-biting or without cross-clamping the aorta.

DR. AZIZ: Did any of the patients have a stroke?

PROF. KLIMA: No.

DR. TRACY: Dr. Hausen?

PROF. KLIMA: May I just make one final comment because there was a lot of discussion going on about this Hanover model I presented today, and a lot of discussion going on with respect with should we use historical controls, yes or no. I think we cannot exclude historical controls because if we just look at the Hanover data with hand-sewn anastomosis compared with an automatic anastomosis and if our hand-sewn anastomosis would have been as bad as the Symmetry anastomosis, we would have concluded that the Symmetry device is as good as the hand-sewn anastomosis, which is absolutely not comparable with this data of the atrial vascularization. So, you have to have a historical control in order to see whether your results really compare to the data of the atrial vascularization out there.

DR. TRACY: Thank you. Dr. Hausen?

DR. HAUSEN: Bernard Hausen. I share Dr. Hirshfeld's concerns. If you look at all these trials that are happening with these devices, 90 percent are done in Europe for a good reason, because you can't recruit American patients to come back and have their angiograms performed at six months or, if you do, you get completion of follow-up of less than 50 percent which Dr. Zuckerman told us is not acceptable. I mean, almost all these trials for American products for American approval are done overseas. I think that is an ethical concern, especially now that there is a class action suit against one of the major valve companies because one of the valves didn't work well and the patients didn't fare well, and now the lawyers in Europe are saying you are putting our patients through all this for the benefit of Americans because we think of all these wonderful trials that involve lots of controls and follow-up. So, I think that is just something we have to put in context here.

DR. WHITE: That is not true. That is absolutely not true. I mean, the European trials clearly precede the American trials, that I won't argue, but we do randomized trials; we do

angiographic follow-up at a very high percentage rate for stent trials for example. So, we do the same thing in the American population that we do in the European population. It just usually lags because of regulatory issues.

MR. MORTON: To echo Dr. Klima's very good point, he has been conducting studies against devices which are CE marked, that is, cleared for marketing, and what we are wrestling with on the panel today is what sort of information do we need before going to 510(k) clearance and that very much affects the sponsors.

MR. LOTTI: My name is Richard Lotti. I am the CEO of Converge Medical. I have some inherent conflicts, of course.

I just want to comment on the last statement regarding trials in the U.S. We are one of the companies that actually did attempt an IDE trial in the United States. We have been successful with it. I will tell you that we had 17 IRB sites approved in the U.S. Over a 12-month period we were able to get 6 sites to enroll patients. During a 3-month period in Germany we were able to get 3 sites to enroll the same amount of patients. So, there clearly are differences in

the two marketplaces, but we believe we have been able to accomplish patients from both geographic centers.

DR. TRACY: Dr. Blumenstein, I think you have some analysis for us.

DR. EMERY: May I make one comment while he is coming up? Dr. Klima raised a very important point in technique because he put the Symmetry device on while a partially occluding clamp was on. I think that is a technical mistake and I am sorry respectfully to do that, but you have to depressurize the system to punch it. You apply the device and then you repressurize the system to aortic pressure and that can disrupt the seating of the device and cause device failure. I think the device was made to be applied in a pressurized system, and varying from that developmental indication can cause problems with the device. So, it may not be a device failure that he suffered through in his bad results but a technical application of the device which alters the way it is implanted.

DR. BLUMENSTEIN: Please keep in mind these are very preliminary, cone by the seat of my pants as I was sitting there.

[Slide]

So, one of the designs we discussed was a paired comparison with a dichotomous outcome. Of course, in any trial one must always identify a primary outcome and in this structure one would define a primary outcome for each vessel graft in each patient and that would be a success or failure. The success, for the purposes of this presentation, is that the graft is okay at the specific follow-up time, say six months. And, you have to define what "okay" is somehow or another and that, of course, is never simple. Failure is not success and that is a way to try to get around missing data but there are still some things I want to say about that.

Within each patient you would randomize two vessels or I suppose four if you could. If you did that, then you have to consider whether you are counting the patient as two units or one. It may require special statistical techniques to handle that situation but for the moment let's assume that we are doing two vessels per patient. One would get usual care, whatever that is, the other would get the experimental intervention.

We have to decide also what to do about

inevaluable patients, that is, patients who don't return for their, say, six-month evaluation. That may not be so bad since you are missing both endpoints but you would, of course, have to assess the reasons the patients didn't come back.

There are lots of complications here. I think I tried to communicate that before. This is a very complicated design. It would be very difficult to administer the randomization, and so forth, and I think we already heard some other people commenting on that. Nonetheless, it might be worth trying.

[Slide]

The basic data structure is a 2 X 2 table. What we would be recruiting would be N pairs of vessels. For each pair of vessels there is an outcome that is either failure-failure, success-success, failure-success or success-failure. So, each of these Ns represents a number of pairs of vessels for which there is both fail, both succeed, etc.

The outcome measure of interest is this number here over this N and this number here over this N, and specifically the difference between those two proportions, that is, this over N and

this over N.

[Slide]

So, these two proportions estimate proportion of success and control vessels and experimental vessels respectively. The statistical test one uses for this is called the McNemar test for testing the difference in these proportions. The required study size depends greatly on the sum of N failed-success and N success-failed, in other words, the discordant cases. If we go back, it is these cases here that represent the difference in outcome within the same patient. Specifically, a smaller proportion of discordant cases leads to a smaller study size.

[Slide]

Now I want to say a word about non-inferiority because that is really I think what we are aiming to test here. We would be testing a null hypothesis of a specified difference. In other words, we would beforehand decide what represented non-inferiority. The alternative hypothesis would be equal or better than inferiority. Rejection of the null hypothesis provides evidence of non-inferiority. I don't happen to have software for planning a

non-inferiority trial for the McNemar test but we can come close to that.

[Slide]

I want to say a word about data monitoring in a non-inferiority trial. A data monitoring committee watches for evidence of rejection of the null and would also look for futility. But early evidence of rejection of the null is easy if the experimental intervention is superior. So, one would put a non-inferiority trial under very tight monitoring if one suspected that there was a possibility of superiority.

[Slide]

The study size computed here is computed for a specified difference of superiority. The non-inferiority study size would be slightly larger. I am sorry, I don't have the software for that. I have assumed an alpha of 0.025 one-sided and a beta of 1.0 or 90 percent power. That is pretty rigorous. I decided to put in the delta, that is, the difference that represented the clinically consequential difference here, of 5 percent.

Now, these are different levels of discordance. That is, this is the proportion of

total patients that are discordant at the end of the trial. So, if we had 20 percent discordant patients the total number of pairs of vessels would be 845. If the discordance was only 10 percent, you are down to a trial size of 420. I personally don't know where in here you would be, or if you were higher or even lower. That is something that would have to be gotten from some other data.

[Slide]

I also did a two-group trial. Being basically a refugee from cancer, I like failure time endpoints so I designed this for a failure time endpoint. Specifically here I said intervention failure-free survival. I just called this AOK. That is alive and okay. You would assess this event continuously or as often as the patient is evaluated immediately post surgery up to whatever is decided to be a reasonable follow-up time.

In particular, you might specifically have time to evaluation, say, at six months as a major evaluation. But the event is a reintervention or death, whichever comes first. Hopefully, you wouldn't reintervene after death. Anyway, this requires a very careful definition of failure.

And, we are designing this again as a non-inferiority trial. I am using an alpha of 0.025 one-sided, beta of 0.9.

[Slide]

If I assume that the proportion of patients in the alive and okay at six months is 75 percent, and just from the data I saw before here in the room that seems like that might be a little low but perhaps not unreasonable considering that we are talking about all kinds of failures, not just failure of the patency of the vessel or occlusion, whatever. So, this is what our control arm would have.

Then we are going to assume that what represents inferiority is a hazard rate, that is a rate of failure that is 20 percent higher than in the control arm. What I get when I do my computation is 1,800 total patients required, randomized in two groups.

[Slide]

Just to give you an idea of what this looks like, this is patients--

DR. WHITE: Are those patients or vessels?

DR. BLUMENSTEIN: Paired vessels--patients.

DR. TRACY: Patients or vessels?

DR. BLUMENSTEIN: Patients, each patient contributing two vessels. So, assuming an exponential distribution, which isn't quite right because I doubt that your failure at two years is this high so if I were going to do this outside the context of this meeting I would probably use a different distribution that would have a plateau here. But we are focusing on this area here, not out here. So, it is going to make a little difference.

The black line represents the control arm. The blue line represents what we consider to be inferiority. The red line represents the critical outcome, assuming the black line is true, of what we would reject and where we would reject given that outcome. So, that gives you an idea of what the inferiority trial would like. You would be looking at this definition between the black and the blue line as representing the criterion for inferiority, but the red line would be the critical outcome assuming the control arm was actually realized. That is it.

DR. HIRSHFELD: Dr. Blumenstein, one generic question about this, for your AOK 75

percent rate I assume that you are looking at a composite rather than a single endpoint. In other words, any one of these trials to generate a 75 percent AOK rate as opposed to a 90 percent AOK rate, we would be looking at a composite endpoint. As a statistician, how do you feel about the use of a composite endpoint as opposed to a single endpoint for analysis?

DR. BLUMENSTEIN: Well, I think it makes a lot of sense in this case because you don't know all the reasons why you would want to discount the experimental intervention. In other words, there could be things happening that you did not anticipate as a result of side effects, and so forth. So, by using a composite endpoint of failure, just simply failure, then you sop up all those bad things that happen that you didn't anticipate. In fact, if you think about it, this is what counts to the patient also. So, the two-group trial has the advantage of pulling together all of those things. It focuses on differences between the groups, whereas the matched study is focused on success with respect to the outcome in the vessels.

DR. HIRSHFELD: Right, although in the

interventional world a composite endpoint has been criticized because some of the components of the endpoint are subject and involve clinical decisions and there is varying of actual clinical significance, and this has led to a great deal of consternation in the interventional arena in terms of the meaning of the composite endpoint that gets virtually into all the interventional device trials.

DR. BLUMENSTEIN: Yes, I mean this is the reality. One would think about setting up an endpoint committee to review the declaration of the endpoints, the timing of them and so forth. I mean, this is not uncommon throughout all of clinical medicine to be discussing endpoints that require some kind of judgment. At least with time-to-event, given that you don't have a lot of issues with respect to interval censoring, that is, frequency of follow-up and so forth, I think you have a gain in precision of using it as a time-to-event rather than as a binary outcome.

DR. BRIDGES: One other study design that you didn't show us is what if we didn't have each patient as their own control but you had two separate groups of patients where, in each case,

all of the proximal anastomoses for example were done with one device, and in the other case all of them were done in the conventional manner, assuming that you typically had two grafts per patient. Would that result in fewer patients being required or a greater number of patients being required, particularly in view of the concerns that have been raised by Dr. Emery regarding the Hanover study design? If we backed up and went to a control group that just had hand-sewn anastomoses and an experimental group that had device implemented anastomoses, how would those numbers work out in that case?

DR. BLUMENSTEIN: Well, that was the second design that I showed you. It would be randomization to a group of patients treated by usual care--

DR. BRIDGES: Sure.

DR. BLUMENSTEIN: --but I used an outcome--

DR. BRIDGES: But you used a single outcome.

DR. BLUMENSTEIN: Yes, I used an outcome that represented time to failure in essence.

DR. BRIDGES: Right, but in this case what

I am suggesting is that you would actually have two outcomes in each patient, the patency of each of the grafts, which would I think decrease the number of patients necessary. In other words, the total number of data points would be twice the total number of patients in that case, whereas, in your study proposed the number of data points is equal to the number of patients, that is, AOK or not AOK.

DR. BLUMENSTEIN: What you are talking about is using a different endpoint than this failure time endpoint, and using an endpoint where you can have multiple observations of that endpoint for each patient. That is a possibility but you then get into issues about what happens if you have missing on one and not the other, or if you have three vessels in one patient and two in the other. You get into some issues like that. They are not difficult terribly but they do cause some kinds of complications. One of the first things that happens is you wonder if the patients who contribute more vessels aren't the ones that were sicker to begin with. So, you have a lot of those kinds of issues. I mean, there are many, many other trial designs that we can talk about.

I thought you were going to ask me about

whether there could be a trial design that had multiple endpoints, for example not only occlusion but also patency and other things of that nature. There are trials that are designed to allow for multiple endpoints, success being defined, say you had five endpoints, meeting three of five. That is a whole other ball game that is very complicated and difficult to get into.

DR. EDMUNDS: That is what I was thinking about, leaving out death because that trumps all endpoints, but a composite endpoint of all of those things that I listed. Is that feasible at all?

DR. BLUMENSTEIN: Well--

DR. EDMUNDS: And mapping that endpoint meets every outcome within the composite having a normal distribution, doesn't it?

DR. BLUMENSTEIN: Well, no, it depends on what you are measuring. You are talking about multiple things contributing to the definition of failure where any one of them can cause a patient to be declared a failure at that moment in time. There is that, plus there is the multiple measurements that one could do. You know, all of these variations lead to different trial designs and different considerations.

The problem that you have when you define multiple endpoints, multiple distinct endpoints is that then you have the weighting issue. Which endpoint is more important than others? For example, in arthritis trials they may have multiple measurements of outcome and they always have the issue of how you weight those things, what is more important.

DR. EDMUNDS: But these cardiology trials usually have death, myocardial infarction and reintervention, or something like that, as a triple composite endpoint. I have always wondered whether that is statistically sound.

DR. BLUMENSTEIN: Oh, I think it is statistically sound. It is statistically sound to consider failure without death. The problem is that you have a hard time making a Kaplan-Meier curve in that case because the Kaplan-Meier curve is them--

DR. EDMUNDS: But death trumps. I would much rather have a myocardial infarction than die. So, they are not equal endpoints and, yet, they are rolled together as a single outcome.

DR. BLUMENSTEIN: Yes, but they make sense to the patient. That is, the patient wants to live

without reintervention so that endpoint as a composite makes sense as a definition of patient benefit. Usually in a trial where you have a composite endpoint you feature as secondary endpoints subsets of events that make up the composite.

DR. EDMUNDS: Well, if it works for cardiologists why doesn't it work for surgeons?

DR. BLUMENSTEIN: Well, I don't know why it wouldn't. I think it would.

DR. TRACY: I think we are sort of addressing question number four, which is should the primary effectiveness endpoint be graft patency alone, or include both graft patency and myocardial perfusion? I think we are looking at trials that are quite large at this point, with a minimum of 420 and a maximum of 1,800 patients, looking at very hard endpoint. I think we would need to try to fine-tune that and see if there really are additional effectiveness endpoints that make some sense in this context so we are not studying devices ad nauseam. Chris?

DR. WHITE: I thought that was great. That was one of the few times I could understand what a statistician has to say, and I think those

numbers are way too big--way too big. I think they are not realistic. I think that is not what this field is used to. I think I would be happy with smaller studies that would satisfy the need and I think we need to come up with ways to make these trials doable in order to provide us with useful information.

DR. BLUMENSTEIN: You are the first physician who has ever said to me that they prefer a smaller trial. I am amazed.

[Laughter]

We statisticians are always in the role of trying to get you to do more than you want to do.

DR. WHITE: I just think that when you look at 400 patients in a trial like this, that is bigger than any trial I can think of, perhaps not drug trials but when you talk about device trials and surgery trials a couple of hundred patients is huge. So, 1,800 is out of the question; 400--I heard four people hit the floor over there; they passed out.

MR. MORTON: It is not so much that anyone wants smaller numbers, we would love to bring larger numbers to the FDA but it is the affordability of the trial.

DR. WEINBERGER: Just one comment, that is something on your slide about the exponential drop-off rate. That is, the earlier you look after the time of implantation, the larger the sample size you will need to show a small difference. As time develops from the original implantation the two curves should splay apart further and one should be able to do the trial with smaller populations to show a meaningful difference. Is that correct?

DR. BLUMENSTEIN: If you are talking about the same difference but at a later point in time, you actually need more patients. The other aspect of this is that there are other causes of graft failure than failure of the proximal connector, and the longer you wait the more those causes come into play and become essentially noise in the data set.

DR. BRIDGES: So, do I interpret Dr. Blumenstein's analysis to suggest that a randomized trial to look at either a composite endpoint or graft patency, certainly in the paradigm of the patient serving as his own control, would require a larger number of patients than we think is appropriate? Then, does that imply that we should take a step back and go to the historical control

issue? Also, as an aside, do you agree with Wolfe Sapirstein's calculations about the number of patients, which is considerably less, that would be required if we use the historical measures such as 80 percent patency for vein grafts and 95 percent patency for mammary grafts?

DR. BLUMENSTEIN: I mean there is nothing wrong--I didn't redo the computations. I assume that the computations were done correctly.

DR. ZUCKERMAN: They were done several times.

[Laughter]

DR. BLUMENSTEIN: But we are using completely different methodologies, different criteria and so forth. They are not completely comparable. But I think the main difference is that the computations shown earlier were based on a single group non-inferiority assessment which suffers from all of the things that one would suffer from by using retrospective data, non-concurrent, randomized controls that is.

So, I think it is very important to first decide whether it is essential, and I think it is personally, to have randomized to control for all of these factors that you can't control and can't

measure and then go on from there. I also want you to remember, and I tried to point this out as I was showing those slides--I was trying to give you an upper bound on the sample sizes. I was using 90 percent power, and so forth, and it is possible that you can trim the sample sizes some. Also, I chose criteria, you know, based on the things that I have seen here today and my best guess at it. It may be that I am using criteria that are too tight. I don't know but this is a beginning.

DR. TRACY: Dr. Edmunds?

DR. EDMUNDS: Would it be irrational to consider any of this list an adverse event and then calculate the number of adverse events for each of the two groups randomized prospectively, and do a power calculation for the occurrence of any one of several adverse events, one per patient maximum, and compare the two at a certain time point? Could that get our N down, and a 5 percent difference rather than 10 or 20? Because we are trying to show equivalency.

DR. BLUMENSTEIN: Well, that is the reason I showed you the two-group non-inferiority trial. In point of fact, the things that went into the definition of what I called AOK could be adverse

events, that is, things that I said--reintervention, that was just a suggestion. You could say that the definition of failure is anything bad that happens, in which case it becomes time to first bad thing. But, you see, in order to preclude the kind of inferiority that I used in those computations, it requires a fairly large trial size.

DR. EDMUNDS: So, the first model was just chi square, wasn't it?

DR. BLUMENSTEIN: It is a McNemar--yes, it is a chi square.

DR. TRACY: I think if you really have an inferior product, by one of these methods you are going to pick it up quicker but if you have something that is not inferior it is going to take longer and it is going to require larger patient populations, and I think there really is an issue here of what is feasible to do; how many patients is it reasonable to include? These are massive trials that we are talking about. I think we either have to come up with a better answer to number four, looking at primary effectiveness, or we have to readdress the idea of historic controls.

DR. BLUMENSTEIN: I want to emphasize that

the two trials that I presented are really quite different in terms of their objectives.

DR. TRACY: Right.

DR. BLUMENSTEIN: They are quite different.

DR. TRACY: Right. I don't think we got an answer here but I think we see what the problems are.

DR. HIRSHFELD: We can answer this question though, can't we?

DR. TRACY: Number four?

DR. HIRSHFELD: Yes. I mean, it is patency, period, isn't it?

DR. TRACY: Number four is should the primary effectiveness endpoint be graft patency alone, or include both patency and myocardial perfusion? I think we have heard that myocardial perfusion doesn't necessarily predict patency. I think patency is a definite primary endpoint. I would think that primary effectiveness is going to in part depend on how large the trial has to be. If your trial has to be enormous, they you accept other pieces of primary effectiveness.

But I think that patency as the dichotomous thing--it is either open or it is

not--is a very important endpoint but the other criteria, such as aortic complications, neurologic changes, hemorrhagic problems, acute revision, all those are other primary effectiveness endpoints in particular for the proximal anastomoses. So, I think you look at your specific device and decide whether there are specific primary effectiveness endpoints that you need to reach. If you are having a 30 percent aortic dissection rate with this particular device, then it is a real problem.

DR. EDMUNDS: I would argue for any adverse event compared between the two groups, and if we find that the adverse events are similar between the two groups then the new device is no worse than what we are doing now, and that really is the question.

DR. WHITE: I disagree. I mean, I understand what you mean but I disagree. I think the endpoint is patency. In fact, the primary endpoint has to be patency; the secondary endpoints can be other issues. But I think the trial, whatever we look at, has to be powered at patency because the experimental device has a direct effect on patency of the graft and that is what we care about.

DR. HIRSHFELD: After all, we are going to measure patency by a fairly sophisticated technique, i.e., angiography. These others are going to require endless hours because they are a continuum. You know, you have good flow; you have bad flow.

DR. EDMUNDS: Yes, but nobody learns anything if the trial is not done because it is so large.

DR. TRACY: If we can move on to number five.

DR. ZUCKERMAN: I think we forgot question number three.

DR. TRACY: Oh, I am sorry. That is true, we did skip that. Number three, do you believe that the significant differences between an arterial conduit and a venous conduit warrant distinct study criteria and assessment for each? If so, please identify these criteria and analyses.

I think the essence was yes, they are different. They are distinctly different, however, the endpoints of patency remain the same whether it is a venous or an arterial structure we are talking about.

DR. ZUCKERMAN: Well, then this helps both

the agency and the industry develop a paradigm. You are saying that a specific indication could be developed for a device intended for the internal mammary and a specific indication could be developed for an SVG device, whether it is proximal or distal, and they are two separate trials.

DR. TRACY: Yes.

DR. ZUCKERMAN: Then, the next question is suppose we are talking hypothetically about an SVG device, the circumflex vessels may behave differently than right-coronary artery. So, what type of distribution or other advice can you give to allow us to have confidence that we don't have to keep slicing and dicing, that we have enough data. Should we have 50 percent RCA, 50 percent circ, or is that too proscriptive, etc.?

DR. WHITE: I think that is too proscriptive. Why doesn't it work to do what we do for stents, and that is that you get data from a stent trial that you then retrospectively look at LAD, circumflex and right because you know there will be a distribution of those? We know from those large trials what the distribution would be. So, I don't know if there is a priori any reason to consider a difference between circumflex and a

right graft. I am not aware that there are differences in patency there. But I would simply do that in a retrospective way, assuming that there would be a good population of patients having both of those grafts done.

DR. EDMUNDS: If you are insisting on patency as the only primary endpoint, you are trying to make this a stent trial and not a surgical trial of an anastomotic connector. And, this is a surgical trial of how to make a connection. It isn't a stent trial and the analogy is not very good. That is why I think there are multiple adverse outcomes and I don't think you can ignore the others just to concentrate on 50 percent or greater patency.

DR. ZUCKERMAN: In general I think the agency would agree with that viewpoint. Even if the sponsor wins on patency but the aortic dissection rate or neurological complication rate is unacceptable, then it is an unacceptable device. We would ask the sponsor up front, even though one of the key sample size calculations would be for the patency hypothesis, to show with what confidence they can rule out some of these other problems because we are looking at multiple key

endpoints. But I guess the question that I have for number three is, is there a big difference between plugging in these grafts with devices to the circ and RCA territories up front that we should be very proscriptive in terms of number of vessels or, as Dr. White has suggested, if you get a fair distribution and then retrospectively it looks like the results are homogeneous, then that is okay?

DR. MAISEL: I think it is one of the factors that goes in with all the other preclinical factors--presence or absence of diabetes, the distal outflow of the graft. I think which vessel it is attached to is equivalent to one of those other factors.

DR. HIRSHFELD: I agree with that. I think that path is an endless path and if you have a hard data point--I agree with Chris, if you have a hard data point that is our goal you can pick up all those other things on an analysis of the data.

DR. EDMUNDS: I think we need to remember that these surgeons are not using these vein grafts to go to the LAD, and there are plenty of people walking around asymptomatic with a patent LAD and nothing else. It is the most important they are

grafting the right and the circ with occasional diagonal branches. We need to consider this in the trial and I think you have to consider multiple endpoints because we have multiple complications which are unique to this device, or so it is alleged.

DR. ZUCKERMAN: Right, and I think we would like other panel members to respond. I think we are in agreement that we are going to consider multiple endpoints but I like your other point that you just made about the importance of LIMA patency for prognosis and survival. Then the implication is if we are looking at separate trials for the LIMA devices versus the SVG devices, are you implying that our delta for non-inferiority for the LIMA trials should be much tighter, say, than for the SVG trials?

DR. HIRSHFELD: I would like to respond to that. I would like to find out first who in the room would have the intestinal fortitude to do a mechanical device LIMA to LAD? I mean, that is the gold standard. I agree with him that there are people running around, myself included, that have LAD grafts that have been patent for 20 years. To say that somebody is going to put a device in there

I think is absolutely wrong. I mean, I would make a condition of the instruments that they exclude the LAD-LIMA.

DR. TRACY: We will take a comment but we are rapidly going to be losing panel members here so if we can try to move along here.

MR. FOLEY: I will try and address that question. I am Mark Foley. I am CEO of Ventrica. Actually, in the trial that we just completed, which was a 100 patient trial with six-month angiographic follow-up, core lab-assessed data and a clinical events committee looking at the MACE endpoints in the trial, we did do LIMA-LADs. We had a 94 percent patency rate in LIMA-LAD. We also did one-year clinical follow-up on the same group of patients. In that group of patients that we followed 46 of 48 were contacted; two were not able to be reached. We had no additional events, no admission to hospital for chest pain, no reoperation, no additional caths in that group.

DR. HIRSHFELD: I think that is terrific but I think you have to follow those people 20 years because the gold standard, as you well know, is LIMA to LAD hand-sewn.

DR. KRUCOFF: Did you have any trouble

enrolling patients?

MR. FOLEY: We didn't. Our trial was done completely in Europe so we were able to enroll patients in the trial. But I would like to ask one more question to Dr. Zuckerman's point, with mammary graft patency will we need to do a separate trial for vein grafts?

DR. TRACY: I am not sure what the answer to that is. I think we are struggling here because the behavior of the vessels is different and the LIMA to LAD is considered the best patency rate that we have. Dr. Aziz, do you have any answer for us?

DR. AZIZ: I think you have said it. I think the biology--you know, the arterial grafts produce prostacyclin and there are a lot of other factors that keep pushing down there so I think at this early stage you should consider them differently. Once you have the data, then I think maybe in the future we may not need to. But at this stage we don't know how the reaction to injury is going to be with some of these new devices. Even though you have shown it is good in the arterial circulation and anastomosis I still think you need to look at it differently.

MS. WOOD: I think I am going to have to insist that we move on to the next question because we are going to lose panel members. We have two more questions to discuss. Let's please make them as brief and to the point as possible for comments, please.

DR. TRACY: Number five, with regard to device safety what criteria, i.e., acceptable adverse event rate, as compared to that for suture should be applied to the evaluation of device safety as distinguished from device effectiveness, for example, myocardial infarction, reoperation, neurologic events and incidence of aortic complications?

DR. EDMUNDS: What is the difference to the patient from a huge stroke? I mean, I don't see the distinction between safety and effectiveness here. Effectiveness, you could argue, is patency but safety is just about everything else.

DR. TRACY: I think safety is, for example, the device ripping off the aorta as the patient stands up the first day postoperatively versus effectiveness, finding a vessel six months out to be patent. So, I think there are some

different safety versus effectiveness endpoints but I think that they should be basically the same safety and effectiveness endpoints as a suture anastomosis would be expected to have. So, I don't think there is a difference between those two safety and effectiveness endpoints.

DR. KRUCOFF: Again, another way to approach this is to start with what is the primary question and what is that going to power to versus what are all the other key concerns about lower incidence events that could happen, and how broad a boundary around those events also would influence thinking about power. You can separate out for a given question a primary endpoint that is effectiveness versus an adequate assessment of safety.

DR. YANCY: And it could be that the better way to do this so we don't struggle is use it as a time-related function, so have group safety and efficacy in one bundle and look at early and then intermediate. That would probably suffice to capture the spirit of the question.

DR. SAPIRSTEIN: Can I just make one point? We make a distinction between safety and effectiveness and it may not be a very hard

distinction, but if we have to re-explore a patient for bleeding and put an extra little stitch in, that is a safety event. If the patient develops a peripheral embolus from the device which still has good patency and the patient gets an infarction in the bed, we call that an adverse event that occurs. Maybe this is not a realistic approach but from the point of view of evaluating these devices we do have to make a distinction between effectiveness and safety.

DR. TRACY: It also becomes difficult to use the patient as their own control because if a patient goes back for a re-bleed for one thing versus another thing, it doesn't matter to that patient, they are still going back for a re-bleed. So, that argues in a way for using historic controls or randomization between a control group and an experimental group but we are seeing that that experimental group might be prohibitively large.

DR. EDMUNDS: You know, if a device comes loose from the aorta, is that effectiveness failure? Is the device not effective? Absolutely. Is it safe? Hell, no.

DR. TRACY: Right. We will move on to

number six, with regard to appropriate patient follow-up, part a), in view of the possible persisting risk of failure of some mechanical anastomosis sites, distinct from progression of native vessel disease, what duration of follow-up is advisable for premarket evaluation?

I think we have sort of addressed these issues. We don't know the biologic activity of some of these things or exactly what the time frame to healing is but we do have to come up with some arbitrary point at which a look is taken, and that might be six months, nine months, something that could be concretely determined as the point at which experience so far tells us that most of the failures would have occurred in the devices that are currently on the market. So, I think we can look at that and decide what that time frame would be for the repeat angio, which seems to be the standard that we are leaning towards for a concrete output.

DR. KRUCOFF: Again, beware of the pitfall that if you look earlier you may see a sign that may or may not be clinically relevant yet. So, if you use a continuous measurement of lumen diameter earlier, that will probably work. If you use a

cut-off, is this a flow-limiting lesion earlier, it may not work and you may really miss something that blossoms later.

The other option to wait until later, you then have more clinical events that will accrue before you look. So, I think you just have to be, again, thoughtful about what is the intention of the trial design as to where you put that and what endpoint you are using, dichotomous or continuous.

DR. TRACY: But, again, in terms of study design it does become difficult to ask a person to come back in a year after an intervention. By that time they have forgotten what you did in the first place so they are not too likely to want to come back. We are already wrestling with a pretty, you know, task-full study.

DR. ZUCKERMAN: Dr. Tracy, I think you have outlined the tensions in this question, but the real question then is, is the stent model applicable, as Dr. Krucoff just said, where routinely there is six-month angiographic follow-up but clinically the patients are followed for another three months to make sure that something seen on the angiogram which may not look significant doesn't portend something down the

road. You know, is there a role for later clinical follow-up?

DR. TRACY: I think we have heard from some of the members that came to speak today that further follow-up is warranted, whether that be by phone follow-up or clinic visit. That probably is appropriate at some point past the angiographic follow-up.

Part b), should postmarket follow-up be required to assess long-term device effectiveness? If so, please define the appropriate length of follow-up after primary patency evaluation.

I don't have a specific time but I do think that out to a minimum of a year with some type of clinical follow-up, whether that is phone contact or office contact.

Number seven, can non-invasive measuring instruments, example, echocardiography, ultrafast spiral CT, MRA, EBT, etc., be used for primary assessment of graph patency or is angiographic follow-up necessary? And, at what time points should patency be assessed? John?

DR. HIRSHFELD: I would like to throw out a suggestion and to get the group to react to it. I think there are three patency variables, acute

patency which is was the graft patent at the time of hospital discharge and the major determinants of that are likely technical. Then there is intermediate patency, which is probably somewhere between three and six months. Then there is late patency, which is six months and beyond.

I would submit that non-invasive imaging, either MR or CT angio, can answer the patency question, and that we should reserve angiography for the time at which we want a morphologic assessment of the actual appearance of the graft. So, one possible paradigm would be to obtain a CT angio or an MR at the time of hospital discharge which would establish the patency of the graft at that point and we probably take technical and acute thrombosis issues off the table at that point. Then, intermediate patency at three to six months could be assessed by another non-invasive imaging study and that might identify candidates for an early angiogram to try to delineate the etiology of the graft failure when graft failure is observed. Then, the late patency would be at six months and that would be an angiographic study.

DR. KRUCOFF: One historical lesson learned just to keep in mind, whenever your

angiographic endpoint is, we have certainly seen that the threshold to reoperate is going to be very high but the threshold to dilate or stent a 75 percent lesion in a completely asymptomatic person once you are in the cath lab, judging by our own history, is going to be very tempting. So, recognize that if you put the angiogram early and don't let people have events you are going to generate events that go with the angiogram. I would suggest that what you do for already enrolling studies maybe we have to take another half step back, but certainly for planning future studies or until we understand the biology of these things in the proximal and the distal locations, which are different, I would suggest pushing out to at least nine months and possibly even a year if the investigators felt it was feasible to get patients back.

DR. TRACY: Chris?

DR. WHITE: I agree with John. My only reservation is that we are asking the non-invasive technology to really step up here. I think that probably those of us around the table who are not absolutely confident that CT or MR is going to give us--at least in our own hands and probably in our

own hospitals, we don't understand the same reliability. But I think the early tests and the screening that we are talking about, it is fine to do it that way as long as the hard endpoint is done with angiography. I think that Mitch is right that late is better but if I was the investigator six months would be where I would really be wanting to do this because I think there is enough activity there. I think we have heard today that the suture lesions in the mammary had calmed down by six months so those sort of things aren't going to be there. And, I think that immediacy to the patient is important. So, I would suggest the six-month angiogram would be okay.

DR. YANCY: I think especially for the use of a non-invasive variable early on, a core lab or a central reading environment really is critical since there is so much more subjectivity about that interpretation.

DR. BRIDGES: Since we are talking about analogies to the percutaneous coronary intervention literature, what is the precedent for the use of non-invasive imaging to assess not graft patency but angiographic patency?

DR. WHITE: Well, in the coronary

circulation it is very early on, as you know. In the peripheral circulation it is an acceptable tool for looking at patency of non-coronary vessels.

DR. BRIDGES: But in the coronary because that is what we are talking about?

DR. WHITE: If we are looking at grafts, I think there is quite a literature about looking at graft patency. I don't think it is unrealistic. I just think that in your hospital you are not going to say that your sensitivity and specificity is 94 percent because you haven't looked at that, and most of us haven't in our own hospitals.

DR. TRACY: I don't think it is most of us in our hospitals, I think nobody has. I just don't think those are established techniques but I think that they do have merit in a trial like this and as an intermediate endpoint I think they are appropriate. Dr. Sapirstein, is there something else that we should be talking about here?

DR. SAPIRSTEIN: No, I think you have helped us considerably and we appreciate that very much. I know there are still a lot of argumentative principles and debate but I think you have given us considerable help.

DR. TRACY: Thank you.

MR. MORTON: Dr. Tracy, one quick comment, back to 6 b), what we would be looking at in 6 b) would be a postmarket--what the panel indicated was that, yes, there would be some further information that you would be interested in at, say, one year. Postmarket surveillance usually is not done on a 510(k) device and what I would suggest is that there could be some creative way of getting the information that you would be interested in perhaps by writing into the clinical protocol that there would be telephonic follow-up, say, at one year, but at the follow-up time of the study the data could be compiled and submitted to the FDA with that phone follow-up to follow. That way we stay out of that unfamiliar regulatory field of postmarket surveillance with a 510(k).

DR. TRACY: I think the spirit of what we want to know is because the biologic activity of these devices is not known, Dr. Krucoff and others have indicated that the six-month look may be premature in terms of finding the true failure rate of these devices. Therefore, some additional follow-up at some later point is appropriate. Now, exactly where in the regulatory process that takes place I am not clear, but I think you need to ask

the patient, "hi, how are you doing? Have you had any chest pain?"

DR. ZUCKERMAN: Dr. Tracy, we are going to clarify that regulatory process for you right now.

DR. HOANG: This is Quynh Hoang, from the Office of Surveillance and Biometrics. I am from the side that does the postmarket. To answer your question, yes, it is possible to request a postmarket surveillance study on even a 510(k) device. The question that we would need is what is the postmarket public health question that you have for the device. It is not limited to the premarket side of how the device was cleared or approved or entered the market. So, I have to stress the adjective or the qualifier of it being a postmarket question, it should not be a question that is required to be answered for the device to be considered acceptable to enter the market. It is a postmarket public health question.

DR. TRACY: I think we are looking for late failures, late clinical failures. So, you are asking the patient how they are; have they had chest pain; have they required reintervention; are they alive or dead.

MS. HOANG: With the question defined,

what we would do would be to go out and it is an order from the FDA to the company to perform a postmarket surveillance study. The one caveat for such a study is that, by law, it is not typically longer than three years. The other one is that the company can come back--we pos the question but the company can come back and offer us different ways. It could be a registry; it could be continued follow-up of the patients that were studied for the premarket application. We would not be prescriptive. We would not identify what study needs to be done. It would be the role of the firm to come back and say this is how we plan to do address the postmarket public health question.

DR. MAISEL: I think that one-year clinical follow-up prior to device approval is not a huge burden given that we are doing a six- or nine-month angiogram.

MS. HOANG: When you put in the statement before device approval you have already cut out the postmarket. This is a question that needs to be addressed after the device already enters the market.

DR. TRACY: But the spirit of why you are doing it at any point, whether it is premarket or

postmarket--and I agree postmarket is appropriate for these devices--is to find out whether there is something you didn't anticipate. I think it is certainly in the company's best interest to adhere to that spirit of finding out whether their product needs improvement. So, I don't see where they would have any objection to a full type of follow-up with very specific questions that really deal with any unanticipated later outcomes.

MS. HOANG: Yes, the only caveat again is that it should not be something that you would need to know before you clear the device because it is a postmarket study.

DR. TRACY: Right, and I think that is why we have to be careful in making sure that our concrete endpoint is at a point where we are comfortable. Even though there is biologic variability, I think we have to just say, given the difficulty in getting patients to come back, we have to accept a six-month invasive follow-up point. Then the postmarket surveillance would be for other unanticipated things to be caught at that point.

DR. BRIDGES: Just a point of clarification, I thought that if a device is

approved under the 510(k) it is either approved or not approved. It can't be approved with a condition based on a postmarket survey. Is that correct?

DR. ZUCKERMAN: I think what you heard is that there should be sufficient data in the application to be able to make a clearance decision. In other words, the major data should be in the application. But then, if there are certain persisting questions or a chronic nature that can be defined, there is a mechanism.

MS. HOANG: That is correct, what Bram just said. it is not a condition of approval. The 510(k) process, Bran can speak to that. I don't believe it allows for conditional approval. But this is a postmarket process that allows for questions that would arise after the device has been out in the market, if there are certain things that occur that cause the agency to wonder whether we should have further studies.

DR. TRACY: I think that the data that we heard at the beginning of the day today indicates that the companies are being very responsive and 90 percent-plus of the problems that we heard about earlier were brought forth by the company. The

companies do not want bad products out there. They are going to do this. I think we are belaboring the point here because there is no company in the world that I can think of that would want to close their eyes if their product is having problems. So, I think it is a moot point, frankly.

DR. YANCY: Dr. Tracy, prior to my departure I just want to make one entry into our record that has to do with a somewhat dissenting opinion about sample size. It seems as if there was a sense of agreement amongst the panel that the sample sizes that were discussed were too large, and it seems to me that with refinement of the protocols we could achieve a sample size in the 400, 500 range. If, indeed, we are talking about 350,000 bypass procedures done per year, we are talking about less than a tenth of a percent to try to get into a study design, and I think that if we are going to be free of these kinds of deliberations in the future the appropriate study design up front is necessary and I, for one, would say what is required is a larger sample size. I would like for it to go on the record that one panel member thinks we should insist on that. I think compromising now sets us up for problems

later.

DR. WHITE: Dr. Tracy?

DR. TRACY: Yes, Dr. White?

DR. WHITE: I think that we all agree with Dr. Yancy as scientists and I think the statisticians say the same thing. The problem is reality and where your cut point is. I think we need to make a decision or we need to make a recommendation that it is not something we are unhappy with and I personally feel very comfortable with a lower bound of 90 percent patency rate. I feel very comfortable that that would be a reasonable device for my father and my grandfather to get for a vein graft anastomosis, and if that can be done with 125 patients, then I think that is not an unreasonable thing. I anticipate currently in many trials the benefit from this OPC criteria that are not randomized and it allows more investigations to be done. It allows more data to be collected, and I think we ought to not put it off just out of hand because it isn't randomized or doesn't meet the highest standards. I acknowledge that but I think there is some compromise that we perhaps can make without compromising data. If we can't do that without compromising data, then I

think Dr. Yancy is absolutely right and we should insist on what we need to answer the questions.

DR. TRACY: I think those are both very fair statements. One more comment and then we will have to move on to the open public hearing. Dr. Bridges?

DR. BRIDGES: My only comment, Chris, is would you be comfortable if your anastomotic device for an internal mammary had a 90 percent patency? Would you be comfortable having someone use that device for your internal mammary artery graft?

DR. WHITE: No, and I think we have all agreed that we have to have two standards for mammary and vein graft.

DR. ZUCKERMAN: But, Dr. White, the calculation that Dr. Sapirstein showed was that the lower confidence limit should be 0.90 for the mammary example. You are now agreeing with Dr. Bridges that that needs to be tightened.

DR. WHITE: I think the mammary needs to be tightened. I think for vein graft patency that would be excellent--

DR. BRIDGES: Right, but that is not on the table. I mean, the issue was that with veins we are talking 80 percent and with mammaries we are

talking 95 percent with a 5 percent delta. So, no one is really talking about a 90 percent vein graft patency. Everybody would be happy with that I think. The issue is with mammaries, is 95 percent the gold standard historically accepting a delta of 0.5; with veins is 0.8 or 0.75 or 0.85, whatever you decide--I don't remember what it was he had put up, it was either 0.85 or 0.8, is it acceptable? So, 0.9 for a vein is really not one of the questions that we were asked to look at.

DR. WHITE: But we get to pick. You get to say what you think would make you happy. These numbers that were put up were simply hypothesis. I mean, they were hypothesis generating. So, we get to say. What I am saying is that I am willing to have a less rigorous scientific design in terms of giving up randomization for vein graft patency of 0.9. Now, perhaps I want patency of 0.98 for a mammary. Again, we get to say what the level of confidence we have is if we are willing to settle for a less severe scientific design.

DR. TRACY: Dr. Ferguson?

DR. FERGUSON: Further than that, we can make the recommendation we want to make but it sounds to me like if we are going to do an

extensive randomized trial on devices that have already been put out there rather than "me too" comparisons we are going back to a PMA format. I am not sure that that is the proper direction. You might want to comment on that.

DR. ZUCKERMAN: Everything that we discussed today can be done through the 510(k) clearance process. There is nothing unusual about doing clinical trials for 510(k)s of this variety.

DR. FERGUSON: Of this magnitude? This size and so on?

DR. ZUCKERMAN: Correct, in the coronary tree. That is correct.

DR. TRACY: At this point I would like to open the afternoon open public hearing. Is there any member of the audience who wishes to address the panel on today's topic? If not, we will close the open public hearing.

I have a serious question for the FDA. It says here on my script that I am supposed to summarize the discussions.

[Laughter]

Do you really want me to do that?

DR. ZUCKERMAN: I know you can do it very well. I will help you if you get into trouble but

I think it would be helpful for us.

Summary

DR. TRACY: I will give it a shot. The first part we discussed, which is obviously difficult thing to grapple with, was the trial design. I think Dr. Blumenstein put together some very nice but very quick analyses of what would be entailed in doing studies with the patients serving as their own controls versus randomized, controlled studies.

The panel expressed concern over the size of the trials that would be required with those designs but does not want to throw out the scientific rigor entirely, but also does not want to throw out the historic information that we have regarding 95 percent patency on the LIMA to LAD. We think that there may be different study designs appropriate if we are dealing with a LIMA versus a saphenous vein graft trial.

We think that the endpoints, particularly dealing with part c) of the first question--surrogate endpoints are not adequate as primary endpoints. The primary endpoint that we think is most reliable is patency. We agree though that there are other design issues that will come

up in some of the later questions. Have I summarized the trial design part adequately?

Moving on to question number two with regard to device placement and device design, please address the following: given considerable differences between the proximal and distal CABG anastomoses, what, if any, differences in study criteria should be required? Again, with the proximal anastomoses devices there are peculiar issues that come up, such as stroke, aortic dissection, etc., that need to be taken into account in the study design, yet the critical endpoint is patency at some point based on the biologic behavior of the anastomoses, and we think that probably six months is an appropriate time frame for that.

We don't think that the endpoint for a proximal anastomosis study versus distal anastomosis study would be different enough to warrant totally different study designs. For example, one shouldn't be studied at 6 months and the other at 12 months. We think that there should be an appropriate failure rate or success rate definable at, we think, 6 months that should be adequately captured with an invasive assessment at

that point.

In terms of determining conduit failure, we recognize that that is difficult to understand, especially since the biology of these devices isn't clearly understood, and we think that a DSMB and core lab would be very helpful in determining these outcomes and analyzing data on a prospective basis.

Question number three, do you believe significant differences between an arterial conduit and a venous conduit warrant distinct study criteria and assessment for each? If so, please identify these criteria. Again, with think that they certainly are biologically very different. The study designs have to take into account, again, the biology of the tissue but also the site of anastomosis but, once again, that patency is the critical outcome that we will be looking for angiographically.

Question four, should the primary effectiveness endpoint be graft patency alone, or include both graft patency and myocardial perfusion? We think that myocardial perfusion may be misleading and we believe primary effectiveness for patency is angiographic follow-up. Other issues, such as aortic disruption have been

mentioned previously. CT and MRI, yes, those endpoints that Dr. Hirshfeld brought up of looking acutely and at intermediate points with CT and MR would probably be appropriate acute and intermediate steps to take.

Number five, with regard to device safety, what criteria, i.e., acceptable adverse events rates as compared to that for suture, should be applied to the evaluation of device safety as distinguished from device effectiveness, example, myocardial infarction, reoperation, neurologic events, we think that the same safety and effectiveness endpoints that pertain to suture should be applied to these devices. We do agree that there is a difference between safety and effectiveness, although there is some overlap in terms of effectiveness but certainly safety issues, such as acute aortic disruption, are safety issues that should, hopefully, be seen only fairly early.

Endpoint evaluation with regard to appropriate patient follow-up, in view of the possible persisting risk of failure of some mechanical anastomosis sites, distinct from progression of native vessel disease, what duration of follow-up is advisable for premarket evaluation?

Dealing specifically with premarket evaluation, we think that that point of angiographic intervention is the endpoint probably for premarket evaluation, and we think that that time point should be somewhere around the six-month time.

Should postmarket follow-up be required to assess long-term device effectiveness? If so, please define the appropriate length of follow-up after primary patency evaluation.

We believe that the answer is yes, there should be some postmarket follow-up. It is in everybody's best interest, in particular the patients. And, that does not have to be a prohibitively complex follow-up process. It could be handled by a phone follow-up.

Number seven, can non-invasive measuring instruments, echo, ultrafast spiral ST, etc., be used for primary assessment of graft patency or is angiographic follow-up necessary? And, at what point should patency be assessed?

I think Dr. Hirshfeld's suggestion that some form of non-invasive assessment acutely and them compared with an intermediate time frame, such as a three- to six-month time frame, would be

appropriate and that could be CT or MR. The late follow-up, however, should be angiographic and that should take place probably at a minimum of six months of follow-up. How is that?

DR. ZUCKERMAN: Fantastic!

DR. HIRSHFELD: Question, Cindy. I didn't hear the final panel recommendation on the study design. I mean, we talked about several of those. Is that something we should talk about or do you know what you want?

DR. ZUCKERMAN: Right, well, what we heard were the pluses and minuses of several different study designs. It is an extremely difficult problem. If there is consensus, we would like to hear about it.

DR. HIRSHFELD: Well, I would just like to mention that the more I think about it--I was initially attracted to it but the more I think about it, the more I would come down on the side against the patients being their own control. We just heard about a trap that it would be too easy to fall into and there must be others, you know, in terms of how the grafts are put on the aorta. So, I don't know if you want to talk about that anymore.

DR. TRACY: Dr. Blumenstein?

DR. BLUMENSTEIN: And another thing about the study design is that I think that anything we do today, at least we have the advantage of hindsight, and any study design considered should be looked at in light of whether it would have detected the problems that you see in the device being marketed. And, I think that is a reasonable standard to apply for future designs.

DR. EDMUNDS: Dr. Blumenstein, is there any way you could use Bayesian statistical models to deal with this? Because I am really concerned that this panel was convened because of concerns about safety and it is more akin to concerns about patency which is, of course, related to safety. But to ignore the fact that, you know, 23 of them popped off and the patients died, and so on, is I think missing the point.

DR. BLUMENSTEIN: Well, I must say this very carefully, when it comes to clinical trials I do not worship at the altar of Bayes.

DR. EDMUNDS: Which altar to you worship at?

DR. BLUMENSTEIN: The altar of randomization, which aren't necessarily completely

disjoint but they are pretty much.

DR. ZUCKERMAN: Okay, but the Center for Devices does also accept Bayesian randomized trials or single-arm trials when appropriately designed up front with our Bayesian statisticians. I am wondering given Dr. Edmunds' suggestion, a lot of times companies come in with European data that perhaps could be used as a prior given that they are going to need to potentially also supply us with U.S. IDE cohort data and it would be an interesting issue to further pursue given that sometimes the Bayesian methodology, if correctly applied, can produce smaller sample sizes. On the other hand, if the prior estimates from Europe are incorrect, the nice thing about Bayesian methodology is that it can produce even larger sample sizes.

DR. EDMUNDS: My concern is that we can shut down a promising innovation by a lot of different people and engineers, and so on, that can actually make an improvement in patient care with advanced coronary-artery disease, particularly if they have advanced aortic disease, atherosclerotic aortic disease, and it is the baby and the bath water.

DR. BRIDGES: I am going to echo Dr. Ferguson's point about the patient serving as his own control. After getting more details on the methodology used in the study in Hanover and thinking about the logistic issues with the sequence of graft placement on the ascending aorta, it seems to me that no matter how you design that study, it would be potentially flawed. So, although I initially thought it sounded like a good idea, now that I understand the details I don't recommend that particular study design.

DR. HIRSHFELD: Since I was the bad guy who initially recommended that, I would just like to go on the record that I agree. I think the advantage of doing the study with that architecture was that you perfectly controlled for most of the within patient variables. However, if doing it perturbs the surgical technique from what would otherwise be practiced, then that is perturbing the entire study.

DR. TRACY: Dr. Zuckerman, were there any additional comments or questions from the FDA?

DR. ZUCKERMAN: The agency greatly appreciates the amount of time put in today by the panel on what has become a very difficult issue,

and I am sure that the agency and industry will benefit from this panel session.

DR. TRACY: Ms. Wells, Mr. Morton, do you have any comments you would like to make at this time?

MR. MORTON: Just congratulations to you. We are ahead of time and covered a lot of territory.

DR. TRACY: All right, at this point we will adjourn the meeting and this concludes the recommendations of the panel regarding the type of data and study required to effectively evaluate performance of aortic anastomotic devices for marketing. Thank you.

[Whereupon, at 4:10 p.m., the proceedings were adjourned.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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